A meta-analysis of the effects of ipratropium bromide in adults with acute asthma

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Authors' objectives
To determine whether inhaled ipratropium bromide provides additional benefits to adults with acute asthma, who are being treated with beta-agonists in an emergency department.

Searching
MEDLINE was searched from 1978 to April 1999 using the following MeSH terms: 'N-isopropylatropine' or 'ipratropium bromide', and 'adult', 'acute asthma' or status asthmaticus'. Searches of Current Contents, the Science Citation Index, and review articles were also performed. Studies were limited to those published in the English language. Details of additional published and unpublished studies were obtained by contacting experts (pulmonologists and emergency physicians) and the manufacturer of ipratropium bromide (Boehringer Ingelheim), and by searching the Medical Editors Trial Amnesty.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing the addition of inhaled ipratropium bromide to treatment with beta-agonists in an emergency department were eligible. The dosing regimes of ipratropium were: once only; twice every 45 minutes to 2 hours; or continuously. The dosing regimes of the beta-agonists were: for fenoterol, once or twice every 30 minutes; and for salbutamol, once or twice every 45 minutes to 2 hours, thrice every 20 minutes, or continuously. The cointerventions included corticosteroids.

Participants included in the review
Adults (older than 16 years) with acute exacerbations of asthma were eligible. The mean age of the participants ranged from 30 to 50 years, and 36% were men. The mean baseline asthma severity ranged from 34% to greater than 40% for forced expiratory volume in 1 second (FEV1), and from less than 30% to less than 45% for peak expiratory flow (PF).

Outcomes assessed in the review
The inclusion criteria for the outcomes were not defined. All studies measured pulmonary function as a continuous variable in terms of FEV1 and PF, and reported them as percentages of the predicted values. The admission rates and adverse events were also assessed.

How were decisions on the relevance of primary studies made?
Two authors independently examined the search and reviewed each identified study according to the inclusion criteria. Any disagreements were resolved by consensus.

Assessment of study quality
Validity was assessed and scored using the following criteria:

- randomisation method, scored 1 (not specified) to 2 (specified);
- demographic characteristics of the sample provided, scored from 0 (none) to 2 (detailed);
- inclusion and exclusion criteria specified, scored from 0 (none) to 2 (detailed);
- asthma definition, scored from 0 (no definition) to 2 (American Thoracic Society criteria used);
sample size calculation, scored from 0 (none) to 2 (detailed); and
withdrawals, scored from 0 (more than 20% of participants) to 2 (none or no more than 20% of participants, with reasons given).

Two reviewers, blinded to the authors and outcome of each study, scored each selected study. The mean score of the two evaluations was divided by the possible score of 12 points, giving values between 0.8 and 1.0. The agreement between reviewers was calculated using a weighted kappa statistic (kappa=0.86).

Data extraction
The following data were extracted: title; author; year and source of publication; the number of patients; the demographic characteristics of the patients; the dosage and route of all medications used; spirometric measure used; the mean and standard deviation of spirometric values at baseline and after treatment; the time of follow-up; statistical analysis; the admission rate; and adverse effects.

The effect of treatment in each study was computed as a standardised effect size for FEV1, if reported; otherwise, PF was used. Each effect size was adjusted for differences in the baseline spirometric measures between treatment groups.

Methods of synthesis
How were the studies combined?
A pooled effect size was calculated as the weighted average of the study-specific sizes using a fixed-effect model, where the weights were equal to the inverse of the variance. The effect size was calculated as close to 90 minutes after initial treatment as possible. The fail-safe N was calculated. The binary outcome of admission rate was pooled using the Mantel-Haenszel technique. The 95% confidence interval (CI) for the pooled odds ratio was calculated using Cornfield's method (see Other Publications of Related Interest no.1). The Breslow-Day test was used to assess statistical heterogeneity. The number of patients needed- to-treat to prevent one admission and the 95% CI were also calculated. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was assessed according to Hedges and Olkin (see Other Publications of Related Interest no.2). A significance level of less than 0.1 (p<0.1) was used to denote heterogeneity. Correlations between the year of publication and methodological quality, and between the effect size and year of publication or methodological quality, were examined. Sensitivity analyses were conducted by excluding five lower quality studies. This limited the analyses to studies of patients with FEV1 or PF less than 35% of their predicted, and to those studies reporting the use of systemic steroids.

Results of the review
Ten RCTs (1,483 patients) were included.

Only 5 RCTs indicated the method of randomisation; 4 RCTs defined the inclusion and/or exclusion criteria in detail; and 7 RCTs included a sample size estimate. The mean methodological quality score was 0.66. There was a significant correlation (rho) between the year of publication and methodological quality (rho=0.76, p=0.02). However, there were no significant correlations between the effect size and year of publication (rho=0.29, p=0.4) or methodological quality (rho =0.42, p=0.2).

Pulmonary function at 90 minutes: the addition of ipratropium to beta-agonist therapy led to a significant benefit. The pooled effect size was 0.14 (95% CI: 0.04, 0.24, p=0.008). The fail-safe N was 36.4. There was no evidence of heterogeneity (p>0.5).

Sensitivity analyses: when the 5 lower quality studies were excluded, the findings were practically unchanged; the results were not reported. For the 4 studies of patients with FEV1 or PF less than 35% of the predicted value, the addition of ipratropium to beta-agonist therapy led to a significant benefit (pooled effect size 0.38, 95% CI: 0.09, 0.67). Systemic steroids had a moderate effect on outcome (pooled effect size 0.14, 95% CI: 0.00, 0.28).
Publication bias: the funnel plot was statistically symmetrical (p=0.58).

Admission rates (5 RCTs, 1,186 patients): the addition of ipratropium to beta-agonist therapy led to a significant reduction in the admission rates. The odds ratio was 0.62 (95% CI: 0.44, 0.88, p=0.007) and the number-needed-to-treat was 18 (95% CI: 11, 77). No evidence of heterogeneity was found (p>0.3). Most papers did not clearly describe their criteria for admission or discharge.

Side-effects (6 RCTs): there were no significant differences between the treatment groups in terms of tremor, heart rate, blood-pressure, respiratory rate, anxiety, dry mouth, or oxygen saturation.

**Authors' conclusions**
The addition of ipratropium to beta-agonist therapy offered a statistically-significant, albeit modest, improvement in pulmonary function, as well as a reduction in the rate of hospital admission.

**CRD commentary**
The aims were stated and the inclusion criteria were defined in terms of participants, study design, and interventions. Searches were conducted for published and unpublished material. By restricting studies to those published in the English language, other relevant studies may have been omitted; this possibility was acknowledged by the authors. The methods used to select the studies were described, and publication bias was assessed. The included studies were limited to RCTs. Validity was assessed and scored using defined criteria, and the methods used to assess the validity were described.

Some relevant details of the primary studies were presented in tabular format, although the method of drug delivery and the criteria used to diagnose acute asthma were not specified. Statistical heterogeneity was assessed and outcomes from the individual studies were presented graphically. A meta-analysis was appropriate given the statistical homogeneity. Sensitivity analyses were undertaken to examine the robustness of the findings.

The evidence supports the authors' conclusions.

**Implications of the review for practice and research**
Practice: The authors state that the addition of ipratropium to beta-agonist therapy offers a statistically-significant, albeit modest, improvement in pulmonary function, as well as a reduction in the rate of hospital admission.

Research: The authors state that future studies should examine whether greater or cumulative doses of ipratropium bromide give any additional bronchodilatation over and above that achievable with beta-agonists. These studies should use standardised criteria for admission or discharge.

**Bibliographic details**

**PubMedID**
10527039

**Other publications of related interest**

This additional published commentary may also be of interest. Peters J. Review: ipratropium bromide with beta-agonists improves pulmonary function and reduces admissions to hospital in acute asthma. Evid Based Med 2000;5:107.
Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Disease; Administration, Inhalation; Adrenergic beta-Agonists /therapeutic use; Adult; Albuterol /therapeutic use; Asthma /drug therapy; Bronchodilator Agents /administration & dosage /therapeutic use; Drug Synergism; Fenoterol /therapeutic use; Forced Expiratory Volume /drug effects; Humans; Ipratropium /administration & dosage /therapeutic use; Middle Aged; Odds Ratio; Randomized Controlled Trials as Topic; Treatment Outcome

AccessionNumber
1199902129

Date bibliographic record published
31/05/2002

Date abstract record published
31/05/2002

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.